2#5

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Bethesda MD 20892

Date: April 23, 1992

From: Director, Center for Biologics Evaluation and Research

Subject: Revised Recommendations for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products

To: All Registered Blood Establishments

INTRODUCTION

On September 25, 1991 the Food and Drug Administration (FDA) licensed the first enzyme immunoassay (EIA) for the simultaneous detection of antibodies to human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2) in human serum and plasma. This test, manufactured by Genetic Systems Corporation, is based on whole viral lysate antigens. Another combination EIA, based on recombinant antigens, and manufactured by Abbott Laboratories, received a license on February 14, 1992. These tests are indicated for detection of antibodies to HIV-1 and/or HIV-2 in human serum or plasma. The tests may be used for donor screening and as an aid in the diagnosis of potential infection with HIV-1 and/or HIV-2.

The availability of licensed screening tests for combined detection of antibodies to HIV-1 and HIV-2 provides blood centers with the capability of performing routine HIV-2 screening without the need to implement a second test in addition to the currently required test for antibodies to HIV-1. Based on this possibility, the issue of whether to recommend donor screening for HIV-2 was discussed at a meeting of the Blood Products Advisory Committee on September 27, 1991.

At the time of the meeting, only 31 cases of HIV-2 infection in the U.S.A. had been reported to the Centers for Disease Control, despite extensive surveillance studies. (One additional case has been reported since then.) These data indicated that HIV-2 infections presently represent only a minimal risk to the safety of the blood supply. Nevertheless, from a public health perspective, use of combination tests offers an opportunity to further protect the safety of blood recipients against HIV-2 infection without requiring an increased number of tests in blood centers. Donor screening for antibodies to HIV-2 would also reduce the need for continued surveillance studies which are expensive, difficult to sustain, and might nevertheless fail to prevent the earliest cases of HIV-2 transmission by blood products.

For these reasons, and with the concurrence of the Blood Products Advisory Committee, the FDA recommends that all establishments collecting whole blood, blood components, Source Plasma or Source Leukocytes implement a licensed test for detection of antibodies to HIV-2 by June 1, 1992. For this purpose the Agency finds acceptable either the use of a licensed combination test for detection of antibodies to HIV-1 and HIV-2 or the use of two separate tests licensed for detection of these antibodies.

To implement HIV-2 testing, modifications are necessary to the current recommendations for the prevention of HIV transmission by blood and blood products. The modifications affect donor selection and deferral procedures, the HIV reentry algorithm, Public Health Service recommendations for additional medical follow-up and counseling, and the management of potentially infectious units from prior collections. For this reason, the FDA is issuing a revised set of recommendations which replaces the Agency's memoranda to blood establishments dated February 5, 1990 and December 5, 1990.

The FDA further discussed donor deferral criteria for HIV at a meeting of the Blood Products Advisory Committee on March 13, 1992. Based on updated scientific data which were presented at this meeting, modifications have been made to some of the deferral criteria. The changes include a 12 month instead of lifetime deferral for sexual partners of persons with high risk behavior, and voluntary instead of recommended use of Confidential Unit Exclusion. Also, the FDA is discontinuing its recommendation for documentation in the donor record of the medical history of HIV associated signs and symptoms.

The revised memorandum also includes reference to use of a licensed immunofluorescence (IFA) test for antibodies to HIV-1 as an alternative to Western blot. On February 5, 1992, Waldheim Pharmazeutika, GmbH, Vienna, Austria was licensed to manufacture and distribute an HIV-1 IFA test which is labeled for use primarily as an additional, more specific test similar to previously licensed Western blot tests.

The revised memorandum does not address the practice of invalidation of aberrant and potentially incorrect screening test results. In past situations, FDA has taken the view that it is not appropriate to invalidate test resu'ts solely on the basis of an unexpectedly high rate of initial or repeat reactive tests. This is because of the possibility that a true positive sample with borderline reactivity could escape detection by a single instead of duplicate retest. Pending a specific recommendation, Blood Establishments are requested not to invalidate test results solely on the basis

of an unexpectedly high rate of initial or repeat reactivity in a test kit. The subject of test invalidation will be discussed at a meeting of the Blood Products Advisory Committee in the near future and specific recommendations in this area will be made following the public discussion.

An addition to the recommendations is an expanded section on "Exclusion/retrieval of potentially contaminated units from prior collections and notification of consignees." This section has been developed in accordance with recommendations of the Blood Products Advisory Committee which were obtained at a public meeting on January 17, 1991. Recommendations and regulations concerning recipient tracing and notification by Transfusion Services are under the authority of the Health Care Financing Administration (HCFA). It is expected that recipient tracing and notification should be carried out by Transfusion Services if the HIV-1 Western blot or IFA is positive on the current donor sample. If the HIV-1 Western blot or IFA is negative or indeterminate, but a second HIV-2 EIA (single virus or combination test) is repeatedly reactive, a medical judgement will be necessary regarding the potential benefits of recipient tracing, especially for units that were collected prior to June 1, 1992.

CLOSING REMARKS

Questions concerning these modified recommendations may be directed to the Food and Drug Administration, Center for Biologics Evaluation and Research, Division of Transfusion Science, Laboratory of Blood Bank Practices, via Telefax number 301-227-6431.

The recommendations contained in this memorandum may be implemented as soon as feasible, without prior approval from the Agency. Upon implementation, licensed blood establishments concurrently should submit a statement for their file indicating that revised standard operating procedures consistent with these recommendations have been put in place. The date for implementation of a routine screening test for HIV-2 should be documented at the blood center and in the license file.

To conform with these recommendations, manufacturers of licensed blood components for transfusion will need to submit an updated circular of information. Manufacturers of Source Plasma or Source Leukocytes will need to submit revised container labels.

for Kathryn C. Zoon, Ph.D.

RECOMMENDATIONS FOR THE PREVENTION OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) TRANSMISSION BY BLOOD AND BLOOD PRODUCTS

Revised April, 1992

TABLE OF CONTENTS

RECOMMENDATIONS FOR THE PREVENTION OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) TRANSMISSION BY BLOOD AND BLOOD PRODUCTS

Revised April, 1992

I. AIDS EDUCATION, SELF-EXCLUSION AND CONFIDENTIAL UNIT EXCLUSION

A. Educational Information to Permit Self-Exclusion

All persons donating blood or plasma for transfusion or further manufacturing use should receive both written information and oral explanation about the safety of blood products in relation to AIDS epidemiology and the implications for donors who have engaged in certain high-risk activities. Donors should not be considered suitable unless information about these risks can be communicated in the language appropriate to each donor (including appropriate communication to persons with impaired vision or hearing) and the educational format is constructed to be culturally sensitive to promote comprehension. The procedures applied should provide an opportunity at each visit for the donor to consider the information and to make an informed and private decision about whether to donate. In some settings it is appropriate to use abbreviated materials for frequent, repeat donors such as autologous donors or serial Source Plasma donors who may be screened as often as twice in a seven day period, and who are familiar with the program employed in the establishment.

Appropriately trained blood establishment personnel should talk with each prospective donor about risk factors for HIV infection. The focus should be on behavior and not on stereotypes. For example, many men who have had male-to-male sexual experiences do not identify themselves as "homosexual," "gay," or "bisexual," but would identify with the description "sex with another man."

The direct questions concerning risk behaviors for HIV infection should be presented to potential donors orally, if possible. The technique demonstrated to be most effective by an FDA sponsored field trial included the use of an illustrated answer sheet for the donor to record a reply as the list of questions (see addendum) was read to the donor. The records for unsuitable donors do not need to include the answers to each of the direct questions about risk behavior, but may indicate that deferral was based on risk behavior history. If the questions are presented orally, the standard operating procedures should ensure that questions are not abridged and each donor record should indicate that satisfactory responses were received. Each donor record should also accurately reflect staff responsibility for this portion of donor screening procedures and document the decision concerning donor suitability or deferral.

The educational material on AIDS should also include a description of HIV associated clinical signs and symptoms including:

- Unexplained weight loss
- Night sweats
- Blue or purple spots typical of Kaposi's sarcoma on or under the skin, or on mucous membranes
- Swollen lymph nodes lasting more than one month
- Persistent white spots or unusual blemishes in the mouth
- Temperature greater than 100.5°F for more than 10 days
- Persistent cough and shortness of breath
- Persistent diarrhea.

It is not necessary for the donor record to include documentation of the donor history for HIV related signs and symptoms. It is necessary that donors be informed about HIV associated signs and symptoms so that they may self-defer if these conditions are present.

B. Criteria for the Exclusion of Unsuitable Donors Who Are at Increased Risk for HIV

The minimum information presented to potential blood and plasma donors at every visit should indicate clearly that persons meeting any of the following descriptions or having engaged in any of the following activities should not donate blood or blood components to be used for transfusion or further manufacturing:

* Persons with clinical or laboratory evidence of HIV (AIDS virus) infection.[1]

* Men who have had sex with another man even one time since 1977.

* Past or present intravenous drug users.

* Persons with hemophilia or related clotting disorders who have received clotting factor concentrates.

* Men and women who have engaged in sex for money or drugs since 1977

---

[1]At this date, the most recent criteria from the CDC appear in MMWR 1987;36(S-1):1-9. A revision of these criteria is anticipated in the near future.

* Persons who have had sex with any person meeting the above descriptions during the preceding 12 months.

* Persons who have had, or have been treated for, syphilis or gonorrhea during the preceding 12 months, or who have had a reactive screening test for syphilis in the absence of a negative confirmatory test in the last 12 months. (Any synonyms for these diseases that may be appropriate to the local donor population should be included in the donor questionnaire and oral interaction.)

  [Note: Refer to FDA's memorandum to all blood establishments dated December 12, 1991 for additional discussion.]

* Persons who have received a transfusion of whole blood, a blood component (e.g. cryoprecipitated AHF, platelets) or a clotting factor concentrate (e.g., Factor IX, Human) within the past 12 months. Receipt of an FDA-licensed plasma derivative other than a clotting factor concentrate (e.g., Albumin [Human]) is not a basis for exclusion.

* Persons born in or emigrating from countries where heterosexual activity is thought to play a major role in transmission of HIV-2 infection (i.e. sub-Saharan Africa and islands located near these areas of Africa[2]) and persons who have had sex with any person meeting the latter description.

  [Note: These criteria should be discontinued upon implementation of a test for antibodies to HIV-2 no later than June 1, 1992.]

Sample direct questions on behavior related to increased risk of HIV infection are provided as an Addendum to this document.

During the health history interview, a donor may volunteer information about a specific instance of possible exposure to hepatitis viruses or to HIV. Suggested deferral periods for two such instances are provided below:

* Persons who have been victims of rape during the preceding 12 months should be deferred.

* Persons who have had contact with blood and body fluids through percutaneous inoculation (such as

---

[2]Sub-Saharan Africa includes all countries of Africa except Morocco, Mauritania, Algeria, Libya, Egypt, Tunisia, Sudan, Somalia and Western Sahara.

injury or accidental needlestick) or through contact with an open wound, non-intact skin, or mucous membrane during the preceding 12 months should be deferred.

Donors should also be informed that:

* There is a time interval early in infection during which tests for HIV may be negative although an infection may still be transmitted.

* A sample of blood will be tested for antibodies to HIV and the donor will be notified if a test is positive (see I.C.1.c); individuals with positive tests will be permanently deferred from future blood or plasma donation.

* The names of people with repeatedly reactive tests for anti-HIV-1 or anti-HIV-2 will become part of donor deferral registries [as required by 21 CFR 606.160(e)].

Information concerning other mechanisms for obtaining HIV antibody tests should be readily available to individuals who may not qualify as donors but who present themselves as prospective donors because of concern about antibody status. Clear instructions concerning alternatives should be available to every prospective donor as well as information about tests to be performed and educational material identifying activities which threaten the safety of the blood supply.

It is also useful to have information readily available to every donor to facilitate prompt notification of the collection center in the event he or she becomes ill or decides the donation may have been inappropriate.

C. Second Exclusion Opportunity

Because of the extreme importance of the self-exclusion process to the safety of blood products, some blood establishments may find it useful to provide a second opportunity to prevent use of a unit from a high-risk donor.

1. Confidential Unit Exclusion (CUE)

Where peer pressure to donate voluntarily may compromise the self-exclusion process, an additional optional procedure can be used whereby a donor may indicate confidentially at the time of donation that his/her blood or plasma donation should not be transfused to others, or used for further manufacturing except as described in I.C.1.d. This procedure is most meaningful if it requires informed and knowledgeable action by every

donor, including autologous donors whose blood might be used homologously, and provides:

a) Strict confidentiality of the donor's decision and privacy in which to make the decision;

b) Assurances to the donor that confidentially excluded units will be tested and the donor notified of any positive test results;

c) Notification to the donor of the results, and counseling or appropriate referral of all donors with positive HIV antibody tests. The criteria for a positive test should be defined in the standard operating procedures of the establishment.

[Note: Pending the availability of licensed additional, more specific tests for anti-HIV-2, notification may be based on a repeatedly reactive HIV-2 EIA, as discussed below in Section II.]

d) Quarantine and destruction of all units designated not for clinical use except in a research protocol or in further manufacture of a special product specifically approved in writing by the Director, CBER. (See I.E.)

2. Private Interview

As another optional procedure to augment self-exclusion, a private interview may be conducted by a trained and competent health professional during which AIDS related educational information is presented orally and the opportunity for self-exclusion is offered. The interview approach has been preferable for paid donors who are unlikely to be responding to peer pressure and whose blood or plasma is intended for further manufacturing use rather than transfusion. Also, because confidential unit exclusion does not preclude donation, the interview technique may be preferred for donors about to undergo lengthy and expensive procedures such as plateletpheresis and granulocytapheresis. In these cases, early assessment of donor suitability may lead to deferral of the donor before the procedure.

D. Donor Consent

The donation records should include a signed consent statement with a provision equivalent in meaning to the following:

"I have reviewed and understand the information provided to me regarding the spread of the AIDS virus (HIV) by blood or plasma. If I am potentially at risk for spreading the virus known to cause AIDS, I agree not to donate blood or plasma for

transfusion to another person or for further manufacture. I understand that my blood will be tested for antibodies to HIV and other disease markers. If this testing indicates that I should no longer donate blood or plasma because of a risk of transmitting the AIDS virus, my name will be entered on a list of permanently deferred donors. I understand that I will be notified of a positive result."

An NIH Consensus Conference which was held in Bethesda, Maryland in July, 1986 determined that it is not ethical to fail to inform donors of test results which resulted in their deferral and/or will result in the discarding of their future collections. For this reason, the Agency believes that blood establishments should notify donors of all positive and indeterminate test results. If, despite the ethical considerations, a blood bank does not intend to notify donors of indeterminate results, the above statement should continue as follows:

"If, instead, the result of the testing is not clearly negative or positive, my blood will not be used and my name may be placed on a deferral list without my being informed, until the results are further clarified."

E. High-Risk Donors

Persons who have engaged in activities that put them at risk of HIV infection may not be donors. However, exemptions may be requested in the form of a specific license application or amendment to permit Source Plasma collection for special purposes, e.g., for research or for manufacture into in vitro products.

Applications requesting additional categories of exemption should include data documenting a need to use donors at increased risk of HIV for the intended product.

Collection of plasma from high risk donors as part of an Investigational New Drug (IND) application, requires a Source Plasma license application or amendment to be filed by the collection facility in addition to the IND filed by the manufacturer of the investigational product.

Special precautions are necessary for collecting, processing, labeling and shipping plasma from high-risk donors for any purpose. Advance approval from the Director, CBER is required for collection of such products [21 CFR 610.45(c)]. An outline of the precautions for handling plasma from high-risk donors may be obtained by writing to the Center for Biologics Evaluation and Research, Congressional, Consumer and International Affairs Branch (HFB-142), Room 1-58, Parklawn Building, 5600 Fishers Lane, Rockville, MD 20857. See also Section III.C. (Labeling and Use of Anti-HIV-Positive Products).

II. LABORATORY TESTING

A. Screening Tests

21 CFR 610.45, requires that blood and blood components intended for use in preparing a product for homologous transfusion or for further manufacturing use be tested according to the manufacturer's instructions and found negative by an FDA licensed test for antibodies to HIV (21 CFR 610.45). Conforming requirements were added to Parts 606, 610 and 640. **Under authority defined in 21 CFR 606.140, as of June 1, 1992, the test(s) for antibodies to HIV are interpreted to include screening test(s) for antibodies to both HIV-1 and HIV-2.**

Whole blood, blood components, or Source Plasma from donors whose samples are found to be repeatedly reactive for antibodies to HIV by an FDA-licensed HIV-1 EIA, an HIV-2 EIA, or an HIV-1/HIV-2 combination antibody screening test should be quarantined and either destroyed or diverted from use in transfusion or further manufacturing unless otherwise approved by the Director, CBER. Establishments which intend to ship units inadvertently collected from donors not known to be positive for anti-HIV must have FDA approved labels and comply with the reporting requirements of 21 CFR 610.45. Exception can be made for use of autologous blood according to recommendations published in memoranda to blood establishments dated March 15, 1989 and February 12, 1990.

The test for antibodies to HIV shall be performed pursuant to 21 CFR 610.45 (b). In all cases except emergencies [21 CFR 610.45 (a)], results must be available at the labeling location before release of the blood product. **The blood establishment that collects the blood is responsible for assuring that appropriate records are maintained and that all FDA requirements are met.**

The following terms apply to HIV antibody testing:

Initially reactive	Initial EIA test is reactive.
Repeatedly reactive	One or both duplicate EIA retests is (are) reactive.
Negative	Initial EIA test is negative or if reactive, both duplicate EIA retests are negative.
Positive	Repeatedly reactive EIA test; Western blot or IFA positive.
Indeterminate	EIA repeatedly reactive; Western blot or IFA neither positive nor negative.

B. Medical Follow-Up, Counseling and Donor Deferral Policies

1. Medical Follow-Up and Counseling

a. The Public Health Service (PHS) has made the following recommendations[3] in regard to testing for anti-HIV-1:

All samples repeatedly reactive for anti-HIV-1 by EIA should be further tested to determine whether the donor is truly positive. These additional tests (e.g., Western blot or IFA) may be done before informing donors of their repeatedly reactive test results.

Because in a blood donor population approximately 90% of repeatedly reactive anti-HIV-1 EIA results are falsely positive, some facilities have delayed notification of persons when additional, more specific tests are not clearly positive, i.e, are indeterminate. Notification of individuals repeatedly reactive for anti-HIV-1 but with indeterminate Western blot or IFA results is recommended because these donors are included in donor deferral registries. This notification should contain information about the significance of the test results, and suggest medical follow-up. If indeterminate patterns are stable for six or more months, in the absence of risk factors, clinical symptoms, or other findings, the individual may be considered negative for purposes of counseling. However, these individuals should be advised that they are not acceptable as donors because of their indeterminate test results. (Donor reentry criteria may apply in some cases, as described in II.C.)

Follow-up of positive results is important both to the public health and to the individual who may be expected to modify behavior to protect intimate contacts. It is strongly recommended, therefore, that donors be notified of all positive test results, and that reporting of results occur in the context of medical counseling.

b. The following points summarize additional PHS recommendations which concern follow-up testing, notification and medical counseling of individuals with repeatedly reactive combination screening tests for anti-HIV-1/HIV-2. (see Figure 1):

Supplemental testing for both HIV-1 and HIV-2 antibodies should be performed prior to notification and counseling. For

---

[3]The PHS recommendations are repeated here for purposes of summarization only. (see MMWR 1985;34:1-5, MMWR 1987;36:509-15, MMWR 1988;36:833-840 & 845, MMWR 1989;38:5-7.)

persons found to be HIV positive for the first time, medical counselors may recommended that a fresh specimen be obtained to verify reproducibility of the test result.

Supplemental testing for HIV-1 should include an additional, more specific test (currently a Western blot or IFA).

i. If a positive result is obtained, the presence of antibodies to HIV is presumed and the donor may be notified and counseled, as described in B.1.a., regardless of the actual virus type.

   For surveillance purposes, additional, more specific testing for HIV-2 can be performed under research conditions on donors who are confirmed positive for HIV-1 antibodies by a licensed Western blot or IFA and who have epidemiological risk factors for HIV-2. These apply to persons born in or emigrating from Sub-Saharan Africa and the nearby islands and to sexual partners of these persons or of known HIV-2 infected persons, as well as to offspring of women in these groups.

ii. If the HIV-1 Western blot or IFA is negative or indeterminate, a licensed EIA test specific for antibodies to HIV-2 and different from the test used for screening should be performed.

   A negative HIV-2 EIA test result may be interpreted to exclude infection with HIV-2. The donor may be notified and counseled based on the HIV-1 test results (see B.1.a.)

   A repeatedly reactive HIV-2 EIA test result may indicate infection with HIV-2. Medical judgement is required to decide what approach to take toward counseling and additional testing:

      The index of suspicion for HIV-2 infection may be based on the presence of epidemiological risk factors for HIV-2, as noted above in B.2.a., or on the specific indeterminate pattern of gag plus pol bands on the HIV-1 Western blot.

      Research studies suggest that investigational tests for HIV-2 antibodies such as Western blot, RIPA, IFA, and synthetic peptide-based EIA may be of value in the interpretation of the HIV-2 screening test result and in providing information useful for counseling the donor. Such supplemental tests should be used routinely when they become available commercially under FDA license.

iii. If a screening test for antibodies to HIV-2 is performed as part of the initial HIV test and is found to be repeatedly reactive, the performance of a second HIV-2

EIA of a different type (either single virus based or HIV-1/HIV-2 combination test) may be useful prior to notification and counseling. If a negative result is obtained by the second HIV-2 EIA, the likelihood of HIV-2 infection is remote. If the second test is also repeatedly reactive, then medical judgement is required to decide what approach to take toward counseling and additional testing, as discussed in the preceding section.

2. Donor Deferral

Donors whose blood samples are found to be repeatedly reactive by screening tests for antibodies to HIV-1, HIV-2 or both viruses should be indefinitely deferred. In some cases, donors may meet suitability criteria for reentry (see below.) Repeatedly reactive screening test results and positive results from additional, more specific tests should be permanently recorded in a way that the donor can be identified subsequently as permanently deferred without disclosing the reason to unauthorized personnel.

Negative anti-HIV test results may be recorded permanently in the individual donor record or the information may be maintained separately, but should be readily available within the collecting facility for verification of negative tests on prior donations. Confidentiality of the results should be protected while, at the same time, it should be ensured that products from unsuitable donors are excluded from use. The deferral system should also ensure that products obtained from subsequent donations of unsuitable donors will not be distributed [21 CFR 606.160 (e)].

C. Donor Reentry

The following algorithm is recommended for reentry of blood donors previously deferred because of a repeatedly reactive test for antibodies to HIV-1 or HIV-2 when screening is performed by individual FDA-licensed HIV-1 and HIV-2 EIA tests, or a single combination test for anti-HIV-1 and anti-HIV-2. The recommended test sequence is outlined in Figure 2 and the criteria for reentry are summarized in Table 1.

A donor may be reentered when test results are as follows:

1. Recommendations for initial screening:

If a licensed HIV screening test is repeatedly reactive, an HIV-1 Western blot or IFA test should be performed on the initial sample. (It is preferable that licensed Western blot or IFA tests be used.) If the repeatedly reactive screening test was an HIV-2 test (single virus or combination test), and if the Western blot or IFA result is negative, then a second, licensed screening test for HIV-2 (either a single virus or combination test) which is different from the original HIV-2 test must also be performed.

a. If a licensed HIV-1 Western blot or IFA is performed, it must be negative.

b. If an unlicensed HIV-1 Western blot was performed, it must not have been positive by the criteria recommended by the Public Health Service (MMWR 1989; 38(S-7): 1-7). If, when indeterminate, the unlicensed Western blot had antibodies to any band among p24, p31, gp41, gp120 or gp160, then a licensed Western blot or IFA must be performed, and must be negative.

c. The second (different) licensed HIV-2 EIA must be negative.

d. If additional licensed screening tests are performed, they must be negative.

2. Recommendations for Tests on a Substituted Sample

If additional testing by Western blot, IFA or additional EIA testing for HIV-2 was not performed on the initial sample as required in 1., or if a licensed Western blot or IFA test proved necessary (1.b), but was not performed on the initial sample, reentry can still be considered provided that a newly obtained sample is "substituted" for the initial sample. Test results on the "substituted" sample must include:

a. A negative licensed screening test using the same test kit (same manufacturer and same product) that was repeatedly reactive on the initial sample.

b. A licensed Western blot or IFA result meeting the criteria described in 1.a or 1.b.

c. A negative result of a second HIV-2 EIA (as described in 1.)

d. If additional licensed screening tests are performed, they must be negative.

3. Recommendations for Follow-Up Testing

Follow-up testing must be performed on a newly obtained blood sample obtained at least six months later than the initial or "substituted" sample, whichever is later. Results of follow-up testing should be as follows:

a. A screening test is negative using the same test kit (same manufacturer and product) with which the initial sample was repeatedly reactive. If the latter test kit is not a whole viral lysate based EIA for HIV-1 antibodies, then the sample must also be tested and found negative by a licensed whole viral lysate based HIV-1 EIA.

b. A licensed HIV-1 Western blot or IFA is negative.

c. A licensed screening test for HIV-2 (either a single virus or combination test) must be negative. If the screening test which was repeatedly reactive on the initial sample was a test for HIV-2 (single virus or combination test), then a second HIV-2 EIA, different from the original test, should be used on the follow-up sample.

4. Exception to the Algorithm

In cases where the test which was repeatedly reactive on the initial sample is no longer manufactured or distributed, it is permissible to test a substituted sample and a follow-up sample using another licensed screening test different from the one that was used on the initial sample.

III. LABELING

A. Products with Negative Anti-HIV Test Results

1. Products for transfusion: The instruction circular must state as required by 21 CFR 606.122(e) that the product was prepared from blood that was negative when tested for antibodies to HIV. Blood establishments should maintain a record of the date of implementation of testing for antibodies to HIV-2.

2. Products for Further Manufacturing Use: The container label should bear the statement, "Negative by a test for antibody to HIV" or equivalent statement. This statement is required by 21 CFR 640.70(a)(11) for Source Plasma and by 21 CFR 606.121(h)(3) for Recovered Plasma. If desired, the statement regarding HBsAg test results [21 CFR 640.70(a)(8)] and anti-HCV test results may be combined with the statement regarding the anti-HIV test results. An acceptable combined statement is, "Negative by tests for antibody to HIV and HCV and nonreactive for HBsAg."

B. Untested Blood and Blood Components

In emergency situations when there is no practical alternative to the release of blood or blood components for transfusion before completion of the required tests, the product(s) must be labeled and shipped in accordance with the provisions of 21 CFR 640.2(f) and 21 CFR 606.121(h).

In the case of rare products which cannot be tested because they were placed in frozen storage before anti-HIV tests were available and for which there is no available substitute product (e.g. rare red blood cell phenotypes), one of the following statements should be applied:

"CAUTION: This product was prepared before testing for antibodies to HIV was implemented and the anti-HIV status of the donor is not known," or

"This product was prepared before testing for antibodies to HIV was implemented. The donor was later tested on ____(Date)____ and found to be negative."

C. Units with Repeatedly Reactive Anti-HIV Test Results

There are currently few approved uses of anti-HIV reactive products other than for research, the preparation of HIV immune globulin/plasma, and the manufacture of reagents required for HIV testing. The collection of plasma for use in such products as well as their manufacture, special labeling and distribution requires advance approval of a specific license application or amendment by the Director, CBER . An outline of special procedures for labeling and distributing such products may be obtained from the Division of Transfusion Science, HFB-900, 8800 Rockville Pike, Bethesda, MD 20892.

Units which are not destroyed should be labeled with two cautionary statements as follows:

"Reactive by a test for HIV antibodies. The risk of transmission of HIV is present."

and

"For further manufacture into in-vitro diagnostic reagents for which there are no alternative sources" or "For laboratory research use only."

IV. EXCLUSION/RETRIEVAL OF POTENTIALLY CONTAMINATED UNITS FROM PRIOR COLLECTIONS AND NOTIFICATION OF CONSIGNEES

The FDA recommends excluding from use previously collected units of blood components or Source Plasma from any person who later exhibits signs or symptoms of AIDS, or later tests repeatedly reactive by a screening test for anti-HIV and does not have a negative licensed Western blot or IFA for antibodies to HIV-1 and a negative licensed EIA for antibodies to HIV-2.

A. Retrieval and Quarantine of Prior Collections

Blood centers should promptly (within 72 hours if possible) identify and quarantine in-date units from prior collections dating back five years whenever a donor has a repeatedly reactive screening test for antibodies to HIV, whether a test for anti-HIV-1, HIV-2, or a combination test. For plasma for fractionation, the identification and retrieval can be limited to units collected in the last six months which have not been pooled or further processed. The consignees of such units should be

notified so that the units that they hold can also be quarantined.

[Note: It is not intended that consignees should initiate recipient tracing based only on a repeatedly reactive donor screening test result and prior to the availability of the result of an additional, more specific test. The purpose of this first notification is to permit blood establishments to take control of units from prior collections so that they will not be transfused or used in further manufacturing pending the result of additional tests.]

B. Release of Units from Quarantine

Units from prior collections that are placed in quarantine may be released if the current (repeatedly reactive) blood, Source Plasma collection is tested by a licensed, more specific test for antibodies to HIV-1 (Western blot or IFA) and the result is negative. If the first, repeatedly reactive screen was a combination test for antibodies to HIV-1/HIV-2, or an individual test for anti-HIV-2, then a second, different licensed HIV-2 EIA (either single virus or combination test) must also be negative.

If the collection occurred more than one year prior to the donor's most recent negative screening test(s) for antibodies to HIV-1 and HIV-2, release can also occur. If the most recent negative screening test for HIV was obtained prior to June 1, 1992, then a negative screening test for HIV-1 alone is sufficient to establish the relevant time period.

C. Notification of Consignees of Additional Test Results

Blood centers should notify consignees of units obtained from the donor's prior collections of the results of additional testing on the donor's current sample. Such testing includes the results of an HIV-1 Western blot or IFA and, if the performed screening included a test for HIV-2, the result of a second EIA for HIV-2. This testing and notification should be completed as soon as feasible (within two weeks if possible) following the repeatedly reactive screening test.

Notification of consignees is performed so that Transfusion Services can carry out recipient tracing and notification (through physicians) if the HIV-1 Western blot or IFA is positive. If the HIV-1 Western blot or IFA is negative or indeterminate, but a second HIV-2 EIA is repeatedly reactive, a medical judgement should be made regarding the potential benefits of recipient tracing. When commercially available, additional tests (other than EIA) for antibodies to HIV-2 may be useful in making this decision.

Figure 1

PUBLIC HEALTH SERVICE RECOMMENDATIONS FOR ADDITIONAL TESTING AND NOTIFICATION BASED ON COMBINATION SCREENING FOR HIV-1 AND HIV-2

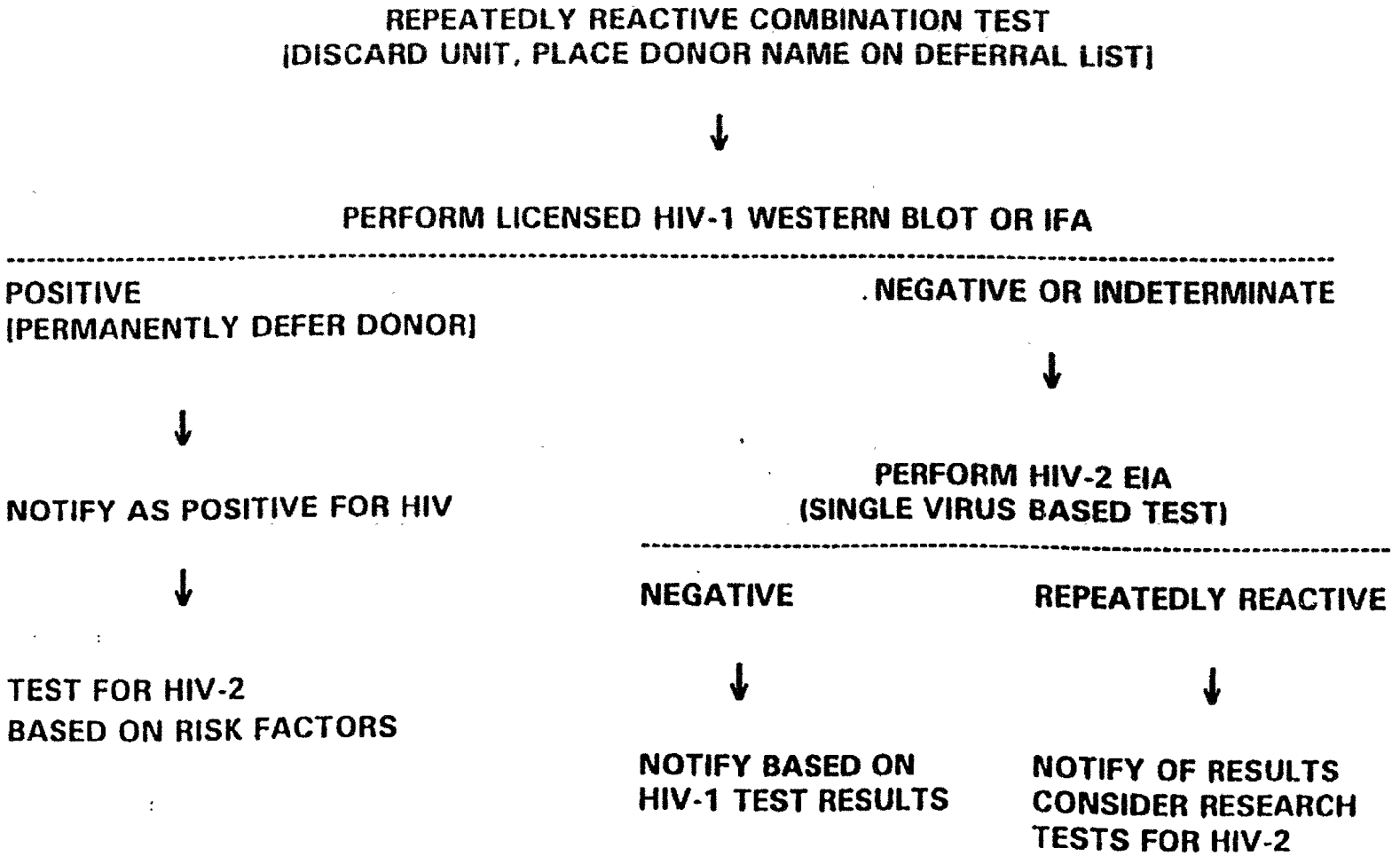
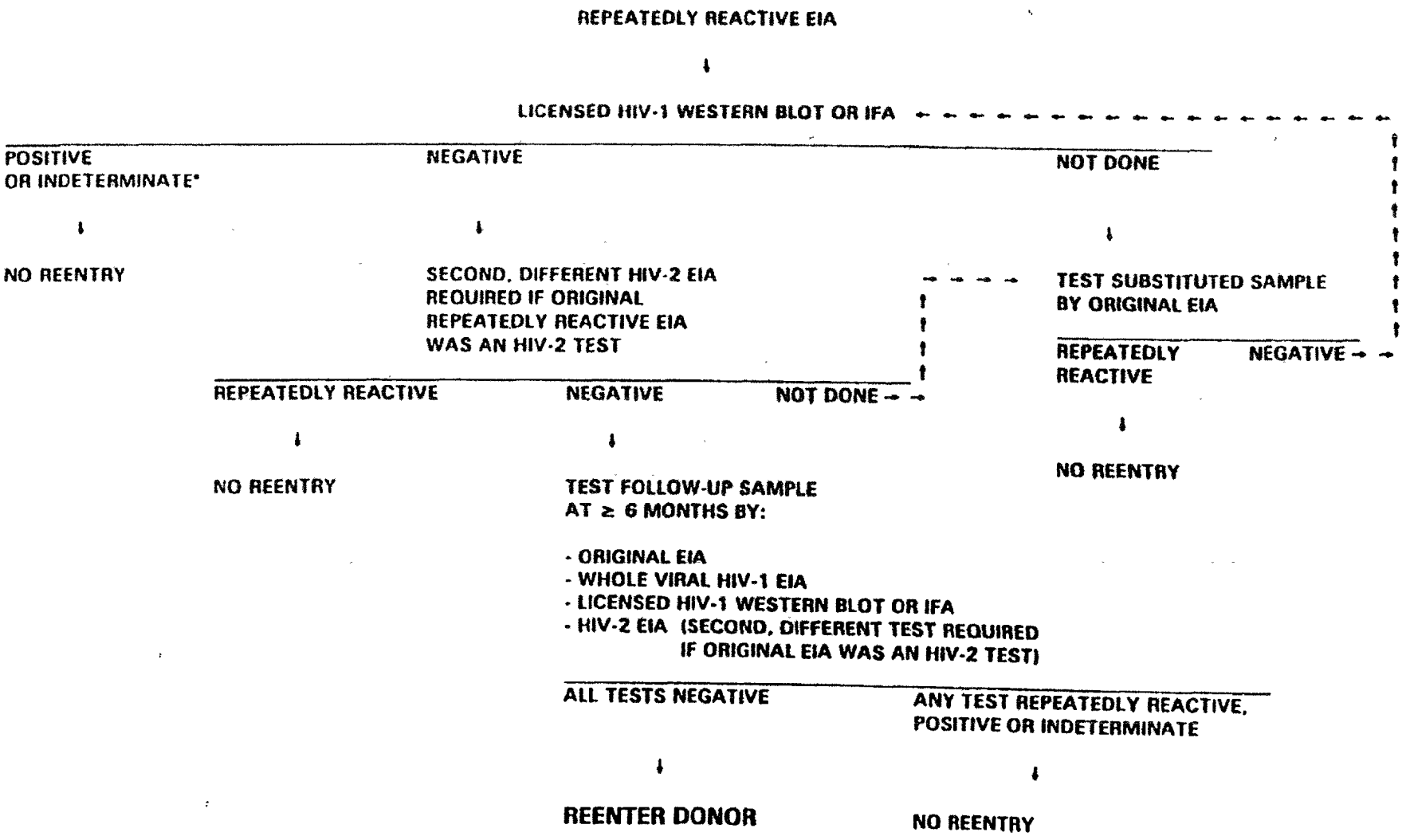


Figure 2

FDA RECOMMENDATIONS FOR DONOR REENTRY FOLLOWING A REPEATEDLY REACTIVE SCREENING TEST FOR HIV



*Special considerations apply to the use of an unlicensed Western blot on the original or substituted sample. See section II.C.1.b. in the text.

Table 1

HIV ANTIBODY TEST RESULTS QUALIFYING A DONOR FOR REENTRY

Test Results

Time	Screening Tests A	B	C	D	Western Blot (WB) or IFA	Second HIV-2 EIA
Initial	RR	ND or NEG	ND[a] or NEG	ND or NEG	ND[b], NEG or INDET (Licensed WB or IFA required if unlicensed WB has a band to p24, p31, gp41, gp120 or gp160. Licensed WB or IFA must be NEG.)	ND[c] or NEG
Sub-stituted	NEG	ND or NEG	ND[a] or NEG	ND or NEG	same as initial sample	NEG
Follow-Up ≥6 mos.	NEG	ND[d] or NEG	ND[a] or NEG	ND or NEG	NEG (must be a licensed WB test)	NEG

[a] If test A is not an HIV-2 EIA or combination test, then an HIV-2 EIA is required

[b] Substituted sample required if test is not done.

[c] Must perform if test A is an HIV-2 EIA (either a single virus or combination test.) If a second HIV-2 EIA is necessary, but was not done, then such a test should be performed on a substituted sample.

[d] Must perform if test A is not a whole viral lysate based EIA test for HIV-1.

See next page for terms and abbreviations used in this table.

Terms and abbreviations used in the table are:

Screening test A	The licensed screening test for HIV-1, HIV-2 or both which is repeatedly reactive on the original sample.
Screening test B	A licensed screening test for HIV-1 different from test A and based on a whole viral lysate antigen.
Screening test C	A licensed screening test for HIV-2 other than test A or test B.
Screening test D	A licensed screening test for HIV other than test A, B or C.
Second HIV-2 EIA	A licensed screening test for HIV-2 that is different from test A (may be a single virus or combination test)
Western blot, WB	A licensed or unlicensed Western blot test for anti-HIV-1.
IFA	A licensed immunofluorescence assay for anti-HIV-1.
ND	Test not done. Performance of the test is optional unless otherwise noted.
RR	Repeatedly reactive screening test.
NEG	Negative test result.
INDET	Western blot test result is indeterminate. CDC criteria apply to unlicensed tests.

ADDENDUM

Sample Direct Questions on High Risk Behavior:

1. Do you have AIDS, or have you ever had a positive test for the AIDS virus (HIV)?

2. Have you ever taken illegal drugs with a needle, even one time?

3. Have you ever taken clotting factor concentrates for a bleeding disorder such as hemophilia?

4.* **Were you born in or did you move to this country from the part of Africa south of the Sahara desert or the islands close to that part of Africa?**

5.* **Have you had sex with anyone who was born in or moved to this country from the part of Africa south of the Sahara desert or the islands close to that part of Africa?**

6. At any time since 1977, have you taken money or drugs for sex?

7. Male donors: Have you had sex with another man, even one time since 1977?

8. Have you had sex in the last 12 months with anyone who has had AIDS or has had a positive test for the AIDS virus?

9. Female donors: In the last 12 months, have you had sex with a man who had sex, even one time since 1977, with another man?

10. Have you had sex in the last 12 months with anyone who has ever taken illegal drugs with a needle?

11. At any time in the last 12 months, have you given money or drugs to anyone to have sex with you?

12. At any time in the last 12 months, have you had sex with anyone who has taken money or drugs for sex ?

13. Have you had sex in the last 12 months with anyone who has taken clotting factor concentrates for a bleeding disorder such as hemophilia?

14. In the last 12 months, have you had syphilis or gonorrhea, or have you been treated for syphilis or gonorrhea? (Add locally appropriate synonyms.)

15. In the last 12 months, have you received blood or blood products by transfusion for any reason, such as an accident or surgery?

Questions 4 and 5 should be omitted following implementation of an FDA-licensed test for antibodies to HIV-2.